08/335,480

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

Abstract of the Disclosure

The optically pure R(-) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(-) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

PATENT APPLICATION
DOCKET NO. SPC89-05

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

Description

Background

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta$_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a

obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(-) isomer of albuterol is administered to an individual who has asthma. For example, R(-) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(-) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(-) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(-) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of

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administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(-) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(-) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(-) albuterol. The two (or more) drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in

tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(-) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(-) isomer may reduce the teratogenic potential associated with albuterol.

Equivalents

Those skilled in the art will recognize, or be able to ascertain, using no more than routine

experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

CLAIMS

1. A method of treating asthma in an individual with albuterol, while reducing side effects associated with albuterol, comprising administering to the individual a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation, said R isomer being substantially free of its S(+) isomer.

2. A method of Claim 1 wherein the amount of the R(-) isomer of albuterol is greater than approximately 90% by weight.

3. A method of Claim 2 wherein the amount of the R(-) isomer of albuterol is greater than 99% by weight.

4. A method of Claim 1 comprising administering to the individual by inhalation from approximately 30 mcg to approximately 90 mcg of the R(-) isomer of albuterol per dose.

5. A method of Claim 1 comprising orally administering to the individual from approximately 1 mg to approximately 8 mg of the R(-) isomer of albuterol two to four times daily.

6. A method of treating asthma in an individual with albuterol, while reducing side effects associated with albuterol, comprising administering to the individual a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation and at least one additional drug.

7. A method of Claim 6 wherein the additional drug is selected from the group consisting of: bronchodilators, antihistamines and analgesics.

8. A method of Claim 7 wherein the analgesic is selected from the group consisting of: aspirin, acetaminophen and ibuprofen.

9. A composition comprising an optically pure R(-) isomer of albuterol and at least one additional drug.

10. A composition of Claim 9 containing at least 90% by weight of the R(-) isomer of albuterol.

11. A composition of Claim 10 containing at least 99% by weight of the R(-) isomer of albuterol.

12. A composition of Claim 9 wherein the additional drug is selected from the group consisting of: bronchodilators, antihistamines and analgesics.

08/335,480

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Declaration for Patent Application

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name;

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

the specification of which (check one)

☐ is attached hereto.

☒ was filed on January 5, 1990 as Application Serial No. 07/461,262 (if applicable). and was amended on _____

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)

(Number) (Country) (Day/Month/Year filed)	Priority Claimed Yes	No
	☐	☐
	☐	☐
	☐	☐

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.) (Filing date) (Status, patented, pending, abandoned)

(Application Serial No.) (Filing date) (Status, patented, pending, abandoned)

As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

I also hereby grant additional Powers of Attorney to the following attorney(s) and/or agent(s) to file and prosecute an international application under the Patent Cooperation Treaty based upon the above-identified application, including a power to meet all designated office requirements for designated states.

David E. Brook	Registration No. 22,592
James M. Smith	Registration No. 26,043
Leo R. Reynolds	Registration No. 20,884
Giulio A. DeConti, Jr.	Registration No. 31,503
Richard A. Wise	Registration No. 18,041
Patricia Granahan	Registration No. 32,227
Mary Lou Wakimura	Registration No. 31,804
Thomas O. Hoover	Registration No. 32,470
Paula A. Campbell	Registration No. 32,503
Alice C. Olek	Registration No. 33,542

all of Hamilton, Brook, Smith and Reynolds, P.C., Two Militia Drive, Lexington, Massachusetts 02173;

and

Send correspondence to: Patricia Granahan, Esq.
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
Two Militia Drive, Lexington, Massachusetts 02173

Direct telephone calls to: Patricia Granahan, Esq.
617-861-6240

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor Timothy J. Barberich

Inventor's Signature Timothy J. Barberich Date 2/23/90

Residence 73 Nashoba Road
Concord, Massachusetts 01742

Citizenship USA MA

Post Office Address SAME

Full name of second joint inventor, if any James W. Young

Second Inventor's Signature James W. Young Date 1 March 90

Residence 295 Still River Road
Still River, Massachusetts 01467

Citizenship USA MA

Post Office Address SAME

Full name of third joint inventor, if any

Third Inventor's Signature Date

Residence

Citizenship

Post Office Address

Full name of fourth joint inventor, if any

Fourth Inventor's Signature Date

Residence

Citizenship

Post Office Address

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	RECEIPT DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
08/335,480	11/07/94	BARBERICH	T 0701,027C

03A1/1216

PHILIP E HANSEN
HESLIN AND ROTHENBERG
5 COLUMBIA CIRCLE
ALBANY NY 12203-5160

0000

12/16/94

NOTICE OF INCOMPLETE APPLICATION FILED UNDER 37 CFR 1.60

A filing date has NOT been assigned since 37 CFR 1.60 has not been complied with for the reason(s) indicated below:

1. ☒ A copy of the specification (description and claims) filed in the parent application:
   a. ☐ is missing.
   b. ☒ has page(s) 2 / 3 missing.
   c. ☐ has the description of the invention missing.
   d. ☐ has claim(s) _____ missing.

2. ☐ A copy of the drawings as filed in the parent application is missing.

3. ☐ A copy of any amendments referred to in the oath or declaration filed to complete the parent application is missing.

4. ☐ A statement is missing that the application papers filed are a true copy of the prior application, and that no amendments referred to in the oath or declaration filed in the prior application introduced new matter. Such statement must be made by the applicant or applicant's attorney or agent and must be a verified statement if made by a person not registered to practice before the United States Patent and Trademark Office.

5. ☐ Other:

The filing date will be the date of receipt of the items required above unless otherwise indicated. Any assertions that the items required above were submitted, or explaining the delay in supplying the omitted items, must be by a petition directed to the attention of the Office of the Assistant Commissioner for Patents. Any such petition must be accompanied by the $ 130 petition fee (37 CFR 1.17(i)(1)). If the petition states that the application is complete, a request for refund of the petition fee may be included in the petition.

All of the items noted above must be submitted within TWO MONTHS of the date of this notice, or the application will be returned upon request or otherwise disposed of.

Direct the response and any questions about this notice to, Attention: Application Processing Division, Special Processing and Correspondence Branch.

A copy of this notice MUST be returned with the response.

Application Processing Division
(703) 308-1202

FORM PTO-1564 (REV. 10-93)

DLEV011843

03LD 12/19/94

0701.027C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Barberich et al.

Serial No.: 08/335,480 Group Art Unit: 1205

Filed: November 7, 1994 Examiner:

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Hon. Commissioner of Patents and Trademarks, Application Processing Division, Special Processing and Correspondence Branch, Washington, D.C. 20231, December 21, 1994.

Philip E. Hansen
Agent for Applicant
Reg. No. 32,700

Date of Signature: December 21, 1994

To: Hon. Commissioner of Patents and Trademarks
Application Processing Division
Special Processing and Correspondence Branch
Washington, D.C. 20231

Response to Notice of Incomplete Application
Filed Under 37 C.F.R. 1.60

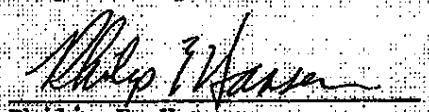
Dear Sir:

This is in response to the Notice of Incomplete Application in the above case. Response is required by February 16, 1995; this response is therefore timely filed. The Notice indicates that the copy of the specification filed on November 7, 1994 was missing pages 2 and 3. Enclosed herewith are copies of pages 2 and 3 and a copy of the Notice.

P:\USERS\PFP\0107\C.RES
December 21, 1994

I hereby verify that the attached pages 2 and 3 are true copies of the latest inventor signed prior application, serial number 08/163,581 as originally filed on December 7, 1993 and further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,



Philip E. Hansen
Agent for Applicants
Reg. No. 32,700

Dated: December 21, 1994

Address for Correspondence:
Philip E. Hansen
Heslin & Rothenberg, P.C.
5 Columbia Circle
Albany, New York 12203-5160
Telephone: (518) 452-5600
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specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

Summary of the Invention

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(-) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent broncho-dilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(-) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is

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administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

Detailed Description of the Invention

The present invention relies on the broncho-dilation activity of the R(-) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(-) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(-) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α[(tert-butylamino) methyl]-4-hydroxy-m-xylene-α, α -diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(-) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
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APPLICATION NUMBER	RECEIPT DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
335,480	11/07/94	BARBERICH T	0701.027C

03A1/1216

LIP E HANSEN
SLIN AND ROTHENBERG
COLUMBIA CIRCLE
ALBANY NY 12203-5160

0000

12/06/94

JAN 9 AM 8:06
GROUP 120

NOTICE OF INCOMPLETE APPLICATION FILED UNDER 37 CFR 1.60

A filing date has NOT been assigned since 37 CFR 1.60 has not been complied with for the reason(s) indicated below:

1. ☒ A copy of the specification (description and claims) filed in the parent application:
   a. ☐ is missing.
   b. ☒ has page(s) 3 missing.
   c. ☐ has the description of the invention missing.
   d. ☐ has claim(s) _____ missing.

2. ☐ A copy of the drawings as filed in the parent application is missing.

3. ☒ A copy of any amendments referred to in the oath or declaration filed to complete the parent application is missing.

4. ☐ A statement is missing that the application papers filed are a true copy of the prior application, and that no amendments referred to in the oath or declaration filed in the prior application introduced new matter. Such statement must be made by the applicant or applicant's attorney or agent and must be a verified statement if made by a person not registered to practice before the United States Patent and Trademark Office.

5. ☐ Other:

The filing date will be the date of receipt of the items required above unless otherwise indicated. Any assertions that the items required above were submitted, or explaining the delay in supplying the omitted items, must be by a petition directed to the attention of the Office of the Assistant Commissioner for Patents. Any such petition must be accompanied by the $_____ petition fee (37 CFR 1.17(i)(1)). If the petition states that the application is complete, a request for refund of the petition fee may be included in the petition.

All of the items noted above must be submitted within TWO MONTHS of the date of this notice, or the application will be returned upon request or otherwise disposed of.

Direct the response and any questions about this notice to, Attention: Application Processing Division, Special Processing and Correspondence Branch.

A copy of this notice MUST be returned with the response.

Application Processing Division
(703) 308-1202

RETURNED WITH RESPONSE

08/335,480

365-201

OMB No. 0651-0031 (12/31/94)

DIVISION-CONTINUATION PROGRAM APPLICATION TRANSMITTAL FORM

ATTORNEY'S DOCKET NO. 0701.027C

DOCKET NUMBER	ANTICIPATED CLASSIFICATION OF THIS APPLICATION: CLASS	SUBCLASS	PRIOR APPLICATION EXAMINER	ART UNIT
0701.027C	514	649	Henley	1205

NOV 7 1994 TECH CENTER

To the Commissioner of Patents and Trademarks:

This is a request for filing a [X] continuation [ ] divisional application under 37 CFR 1.60, of pending prior application serial no. 08/163,581 filed on December 7, 1993, of Timothy J. Barberich and James W. Young for Method for Treating Asthma Using Optically Pure (R)-Albuterol.

1. Enclosed is a copy of the latest inventor signed prior application, including the oath or declaration as originally filed. I hereby verify that the attached papers are a true copy of the latest inventor signed prior application serial no. 08/163,581 as originally filed on December 7, 1993, and further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Claims	(1) For	(2) Number Filed	(3) Number extra	(4) Rate	(5) Calculations
	Total Claims	12 - 20=	0	X $22.00	$
	Independent Claims	3 - 3=	0	X $ 76.00	
	Multiple Dependent Claim(s) (if applicable)			+ $ 240.00	
			Basic Fee		+ $730.00
			Total of above Calculations =		
	Reduction by 1/2 for filing by small entity (Note 37 CFR 1.9, 1.27, 1.28) if applicable. Affidavit must be filed also.				- 365.00
			Total National Fee		$ 365.00

2. [X] The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 08-1935. A duplicate copy of this sheet is enclosed.

3. [X] A check in the amount of $ 365.00 is enclosed.

4. [ ] Cancel in this application original claims _____ of the prior application before calculating the filing fee. (At least one original independent claim must be retained for filing purposes.)

5. [X] Amend the specification by inserting before the first line the sentence: This application is a [X] continuation, [ ] division, of application serial no. 08/163,581, filed 12/7/93.

6. [ ] Transfer the drawings from the pending prior application to this application and abandon said prior application as of the filing date accorded this application. A duplicate copy of this sheet is enclosed for filing in prior application file. (May only be used if signed by person authorized by § 1.138 and before payment of issue fee.)

FORM PTO-FB-A420 (10-94) Page 1 of 2 Patent and Trademark Office - U.S. DEPARTMENT of COMMERCE

DLEV011849

a. ☐ New formal drawings are enclosed.

b. ☐ Priority of application serial no. _____ filed on _____ in

_____ (country) is claimed under 35 U.S.C. 119.

☐ The certified copy has been filed in prior application serial no. _____

; filed _____.

7. ☒ The prior application is assigned of record to Sepracor, Inc.

8. ☐ A preliminary amendment is enclosed.

9. ☒ A verified statement claiming small entity status is enclosed in parent application Serial Number 08/163,581, filed December 7, 1993 and is still proper.

10. ☐ Also enclosed _____

11. ☒ The power of attorney in the prior application is to

Hamilton, Brook, Smith and Reynolds, P.C.; an Associate Power of Attorney to Philip E. Hansen was filed July 14, 1993

a. ☒ The power appears in the original papers in the prior application.

b. ☐ Since the power does not appear in the original papers, a copy of the power in the prior application is enclosed.

c. ☐ Address all future communications : (May only be completed by applicant, or attorney or agent of record)

Philip E. Hansen, Heslin & Rothenberg, P.C.

5 Columbia Circle

Albany, NY 12203-5160

11/7/94 (date) (signature) Philip E. Hansen

Address of signator: ☐ inventor(s) ☐ filed under 1.34(a)

☐ assignee of complete interest

☒ attorney or agent of record

5 Columbia Circle

Albany, NY 12203-5160

Paper No. 4 (IDS)

11/7/94 IS MISSING?